Nonformulary Criteria for Use
Dronedarone
May 2010
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

The manufacturer's labeling and/or the VA National PBM-MAP-VPE Dronedarone Drug Monograph at www.pbm.va.gov or http://vaww.pbm.va.gov should be consulted for detailed information when prescribing dronedarone.

Background:
In the pivotal ATHENA trial, treatment with dronedarone reduced first hospitalization for cardiovascular events or death compared to placebo in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL). There was no significant difference compared to placebo in all-cause mortality. Dronedarone is contraindicated in patients with NYHA class IV heart failure (HF) or NYHA class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic based on data from the ANDROMEDA trial where there was an increase in mortality with dronedarone compared to placebo; this trial enrolled patients with moderate to severe HF and recent decompensation and did not specifically study patients with AF/AFL. When compared to placebo in patients with AF, dronedarone reduced the time to AF recurrence; however, results from one unpublished clinical head to head trial of dronedarone versus amiodarone showed that dronedarone was not as effective as amiodarone in reducing recurrence AF. Dronedarone is a derivative of amiodarone, exhibiting similar pharmacologic effects, and was designed to reduce the potential adverse effects seen with amiodarone. In the ATHENA trial, there was no significant difference in the reporting of pulmonary or thyroid effects compared to placebo; although, the authors note that the trial may not have been long enough to conclude that dronedarone has a safer side effect profile (especially pulmonary) compared to amiodarone. Published head to head trials are needed to determine the efficacy and safety of dronedarone in comparison to other available antiarrhythmic agents used in the management of patients with AF/AFL.

VAMedSAFE:
Due to potential safety concerns for new onset or worsening HF in certain patient populations, unknown long-term pulmonary toxicity, and VA reports of a probable drug interaction with warfarin, VAMedSAFE has implemented an ongoing analysis of patients treated with dronedarone to monitor for these safety signals.

FDA Approved Indication:
Dronedarone is an antiarrhythmic agent approved by the FDA to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age > 70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter $\geq$ 50mm or left ventricular ejection fraction [LVEF] < 40%), who are in sinus rhythm or who will be cardioverted.

EXCLUSION CRITERIA (if ONE is checked, patient is not eligible)

- ☐ New York Heart Association (NYHA) Class IV heart failure (HF) or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic (Boxed Warning)
- ☐ Second or third degree atrioventricular block or sick sinus syndrome (except in conjunction with a pacemaker)
- ☐ Significant bradycardia (e.g., < 50 bpm)
- ☐ Receiving concomitant strong CYP 3A inhibitor (e.g., ketoconazole, itraconazole, voriconazole, cyclosporine, telithromycin, clarithromycin, nefazadone, and ritonavir)
- ☐ Uncorrected hypokalemia or hypomagnesemia
- ☐ QTc Bazett $\geq$ 500 ms with appropriate correction for prolongation of QRS interval in patients with intraventricular conduction delay and ventricular pacing
- ☐ Receiving concomitant medications that may prolong the QT interval and increase the risk of torsade de pointes (e.g., phenothiazine antipsychotics, tricyclic antidepressants, certain oral macrolide antibiotics, Class I and III antiarrhythmic agents)
- ☐ Severe hepatic impairment (i.e., Child-Pugh Grade C or baseline LFTs > 2 X upper limit normal[a])
- ☐ Long standing (> 1 year duration) atrial fibrillation without proven successful cardioversion, unless patient is being considered for cardioversion
- ☐ Pregnancy (Category X)
- ☐ Nursing mothers[b]

INCLUSION CRITERIA (must fulfill ALL the following to be eligible)

- ☐ Initial prescription restricted to VA Cardiology or local designee (monitoring must be documented by a VA provider)
- ☐ Symptomatic recurrent paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL) documented by ECG within the past 6 months, with a second ECG in sinus rhythm or pending cardioversion
- ☐ Intolerance (e.g., unmanageable significant adverse event), contraindication to, or ineffective therapy with at least one other antiarrhythmic agent used for the rhythm management of AF (refer to pharmacologic management considerations for AF in the table below)

Considerations for Pharmacologic Maintenance of Sinus Rhythm in Patients with Recurrent Paroxysmal or Persistent AF[1,2]				
	No or minimal structural heart disease	**Hypertensive heart disease with substantial LVH**	**CAD**	**HF[6]**
First line therapy[3]	Flecainide Propafenone Sotalol	Amiodarone Dronedarone[4]	Dofetilide Sotalol	Amiodarone Dofetilide
Second line therapy	Amiodarone Dofetilide Dronedarone[5]		Amiodarone Dronedarone[5]	

[1]Adapted from ACC/AHA/ESC 2006 guidelines for the management of patients with AF. Circulation 2006;114:e257-e354
[2] Recommendations are not intended for switching patients who are stable on current therapy
[3] One or more of the agents listed should be considered prior to considering second line therapy; treatment selections listed alphabetically, not in order of preference
[4]Dronedarone is Nonformulary in the VA. Dronedarone may be an alternative in patients who are intolerant to the recommended first-line VA National Formulary treatment with amiodarone in this patient population; in addition, dronedarone may be considered prior to amiodarone in a younger (e.g., < 60 years of age) patient on a case by case basis, subject to local adjudication
[5]Dronedarone is Nonformulary in the VA; medications on the VA National Formulary should be considered prior to treatment with Nonformulary agents. Dronedarone may be considered prior to amiodarone in a younger (e.g., < 60 years of age) patient on a case by case basis, subject to local adjudication
[6]Dronedarone is contraindicated in patients with NYHA Class IV HF or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic (Boxed Warning); the safety of dronedarone in patients with AF and LVEF ≤ 35% is unknown: inclusion criteria for ANDROMEDA approximated LVEF ≤ 35%, and found an increase in mortality with dronedarone vs. placebo; only ~ 12% patients included in ATHENA had LVEF < 45% with subgroup evaluation in patients with LVEF < 35% (~4% of patients enrolled) that did not find a difference between dronedarone and placebo in the primary endpoint of first hospitalization due to CV events or death. As the LVEF may fluctuate in patients with AF (i.e., LVEF may fall into the range that puts a patient at high risk), this should be taken into account when considering treatment with dronedarone

For women of childbearing potential,

☐ serum pregnancy test should be performed prior to receiving dronedarone

☐ use of an effective method of contraception during dronedarone therapy

DOSING RECOMMENDATIONS

- The recommended dose of dronedarone is 400 mg administered twice daily with the morning and evening meals

MONITORING

- Assess for adequate symptom control (e.g., frequency or duration of palpitations/irregular heartbeat, time to recurrence)
- Evaluate for signs or symptoms of new or worsening HF; risk for serious adverse events unclear in patients who may experience transient decreases in ejection fraction
- ECG for QT prolongation (dronedarone should not be used if QTc Bazett ≥ 500 ms)
- ECG for normal sinus rhythm; dronedarone should not be used for treatment of long standing (> 1 year duration) atrial fibrillation without proven successful cardioversion; if patient remains in atrial fibrillation while on dronedarone, they should be referred back to and/or provider should consult with Cardiology
- Heart rate for bradycardia (it is recommended that dronedarone be discontinued if significant bradycardia; e.g., < 50 bpm)
- Serum electrolytes for hypokalemia or hypomagnesemia, if receiving potassium depleting diuretics
- Serum creatinine for potential increase of 0.1 mg/dl (reported to plateau 7days after initiation; without an effect on GFR)
- Dronedarone should be used with caution in patients with moderate hepatic impairment (i.e., Child-Pugh Class B) due to an increase in dronedarone exposure with wide variability in drug exposure that may increase the risk for adverse events. These patients should be monitored closely for increase in liver enzymes (AST/ALT) > 2 X upper limit normal[b] and > 0.5 X upper limit normal from baseline values
- Drug Interactions
  - *Warfarin:* although there was no clinically significant increase in INR in a single-dose study in healthy individuals administered dronedarone in conjunction with warfarin, additional monitoring and/or dose adjustments of warfarin may be warranted in patients receiving dronedarone given VA ADERS reports of a probable drug interaction with elevated INRs and bleeding
  - *CYP 3A inhibitors or inducers:* in addition to being contraindicated in patients receiving concomitant strong CYP 3A inhibitors (refer to exclusion criteria), it is recommended that dronedarone not be administered with moderate CYP 3A inhibitors (e.g., diltiazem, verapamil, grapefruit juice) or CYP 3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort)
  - *Substrates of CYP 3A, 2D6, or P-glycoprotein (P-gP):* dronedarone may inhibit P-gP, and is also a moderate inhibitor of CYP 3A and CYP 2D6 and can therefore interact with substrates of these enzyme systems including some statins (it is recommended that the labeling recommendations be followed according to the respective statin for use with CYP 3A and P-gP inhibitors), sirolimus, tacrolimus and other medications metabolized by CYP 3A; beta-blockers, tricyclic antidepressants, SSRIs metabolized by CYP 2D6. If dronedarone is used in combination with digoxin (P-gP substrate), it is recommended the dose of digoxin be halved; monitor digoxin levels and for toxicity
- Discuss risk vs. benefit of therapy in patients of child-bearing potential and appropriate methods of contraception

RECOMMENDATIONS FOR DISCONTINUATION

- Patient does not experience adequate symptom control (e.g., no or inadequate change in frequency or duration of palpitations/irregular heartbeat; no or inadequate increase in time to recurrence AF/AFL)
- Patient experiences a significant drug related adverse event

[a] Dronedarone has not been studied in patients with baseline LFTs > 2 X upper limit normal
[b] It is unknown if dronedarone is excreted in human milk; due to the number of medications that are excreted in human milk and the potential for serious adverse reactions that may occur if a nursing infant is exposed to the drug, the risk vs. benefit of whether the mother should discontinue nursing or to begin dronedarone should be discussed